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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/058,456	01/28/2002	Pascale Pouzet	1/1168	4239

28501 7590 10/16/2003

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,456	POUZET ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears n the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-18 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-18 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-8, 11-18 and 21-28 are currently pending in the instant application and are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6 August 2003 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Response to Amendment

The Declaration of Hisato Kitagawa under 37 CFR 1.132 filed 6 August 2003 and signed 23 July 2003 is insufficient to overcome the rejection of claims 1-8, 11-18 and 21-28 based upon 35 USC 103 as set forth in the previous Office actions because:

It is applicant's burden to demonstrate unexpected results over the closest prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

The Declaration of Hisato Kitagawa does not demonstrate unexpected results over the closest prior art. The declaration compares 2 compounds of applicants instant invention: 5'-chloro-3'-isopropyl-2'-methylphen-1'-yl-2-iminoimidazolidine (example 27) and 3'-tert-butyl-6'-methoxyphen-1'-yl-2-iminoimidazolidine (example 2) with one compound of WO 96/32939: 2-(6'-bromo-3'-dimethylamino-2'methylphenylimino)imidazolidine (example 2). However, 2-(6'-bromo-3'-dimethylamino-2'methylphenylimino)imidazolidine is not the closest prior art because

this compound contains two differences from the instantly claimed invention, first, the variable R2 in the instant claimed invention cannot be dimethylamino and , second, this compound does not have a branched alkyl in positon R2 or R4. The closest prior art is the compounds of (lines 18-26, column 11 US and page 17, lines 18-26 WO), specifically 2-(2-chloro-3-methylphenylimino)-imidazolidine from WO 96/32939 which differs from applicants claimed invention by having methyl instead of a branched alkyl at position R2 and the compound of 2-(2-bromo-6-chloro-4-isopropylphenylimino)-imidazolidine (page 2, line42) from DE 3712385 which differs form applicants claimed invention by the position of the isopropyl (position R3 instead of position R4 or R2). Furthermore, the declaration fails to demonstrate unexpected results over the closest prior art because although the declaration states that the Pouzet et al. application possesses unexpectedly superior metabolic stability and higher bioavailability, it does not compare the closest prior art and does not show the results for tests A and B which show metabolic stability. Finally, the declaration only compares two examples of applicants instantly claimed invention with one compound of the prior art, which is not a reasonable scope commensurate in scope with the claimed subject matter. Therefore, since the declaration fails to compare the closest prior art, fails to disclose the results for the compared art for the metabolic stability tests and fails to be of a scope reasonably commensurate with the scope of the subject matter claimed, the declaraion is insufficient to overcome the rejection of claims 1-8, 11-18 and 21-28 based upon 35 USC 103 as set forth in the previous Office actions.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

Claims 1-8, 11-18 and 21-28 are rejected under 35 USC 103(a) as being unpatentable over WO 96/32939 and DE 3712385. The English equivalent of WO 96/32939 is the national stage entry of PCT/EP96/015868, US Patent No. 6,268, 389. Page numbers in both the WO and US Patent will be provided in the discussion of the contents of the prior art. The rejection of claims 1-8, 11-18 and 21-28 under 35 U.S.C. 103(a) as being unpatentable over WO 96/32939 and DE 3712385 is MAINTAINED for essentially the same reasons as set forth in the Office Action mailed 26 August 2002, Paper No. 6 and in the office action mailed 3 April 2003. This rejection might be overcome by submitting a sufficient 37 C.F.R. 1.132 declaration showing the unobvious and unexpected superiority of the selective activity on the bladder without substantially affecting the cardiac circulatory system and the unexpected superiority in regards to

bioavailability and metabolism over the closest prior art compounds as found in WO 96/32939 and DE 3712385.

The instant claims teach alpha-1-agonist alkylphenyliminoimidazolidine tautomeric equivalent derivatives of formulas I and II (claims 1-8), which are useful in pharmaceutical compositions (claims 11-18) for the treatment of urinary incontinence (claims 21-28). The compounds of formulas I and II can be substituted in the R1, R3 or R5 position by hydrogen, bromine, or chlorine (claims 1-8) and R2 and R4 must have one of the groups being a branched C3-6-alkyl (claim 1) such as tertiary butyl or isopropyl (claims 2-8).

Determining the scope and contents of the prior art

WO 96/32939 discloses phenlyiminoimidazolidine tautomeric equivalent derivatives of formulas Ib and II (WO page 2 line 19- page 3 line 22, US column 2 lines 5-50), which are useful in pharmaceutical compositions (WO page 18 line 15-24, US column 11, line 52-64) for the treatment of urinary incontinence (WO page 1 lines 1-3, US column 1 lines 11-13. Preferred compounds of formulas Ib can be substituted at positions R1, R2, R3, and R5 with hydrogen, bromine, chlorine and R4 can be C1-4 alkyl (WO page 4 lines 11- page 5, US column 3 lines 5-33). Alkyl is defined as branched or unbranched alkyl groups such as isopropyl and tertiary butyl on page 6 lines 13-18 of WO 96/32939 (US column 4, lines 4-9).

DE 3712385 discloses phenyliminoimidazolidine derivatives of the formula I (page 2, lines 5-10), which are useful in pharmaceutical compositions (page 6) as an

alpha1-adrenergic agonist (page 4 line 22). A specific compound disclosed is 2-(2-bromo-6-chloro-4-isopropylphenylimino)-imidazolidine (page 2, line42)

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art WO 96/32939 and the claims at issue is that the prior art generically encompasses that which is instantly claims and discloses preferred embodiments encompassing that which is instantly claimed but does not make a specific compound that falls within the invention as instantly claimed. The difference between the prior art DE 3712385 and the claims at issue is that DE 3712385 discloses a positional isomer of the compounds as instantly claimed.

Resolving the level of ordinary skill in the pertinent art

However, it would have been obvious to someone of ordinary skill in the art at the time of the invention when faced with the prior art to create compounds as instantly claimed wherein R2 or R4 must have one group being a branched C3-C6 alkyl. The motivation to make the claimed compounds derives from the expectation that the instant claimed compounds would possess similar activity to that which is disclosed in the prior art discussed above. The motivation would come from the disclosure of preferred embodiments of the compound of formula Ib, which is useful for the treatment of urinary incontinence, in WO 96/32939 which prefers R4 being a C1-C4 alkyl and R1, R2, R3, and R5 as hydrogen, bromine, or chlorine and the disclosure of a positional isomer of the compounds as instantly claimed in DE 3712385 which are useful for the treatment of urinary incontinence. In regards to DE 3712385, nothing unobvious is seen in substituting the known claimed isomer for the structurally similar isomer, since such structurally related compounds suggest one another and would be expected to share

common properties absent a showing of unexpected results. Compare rational in In re Norris, 84 USPQ 458 (1950). Additionally, since applicant is claiming a method of treating urinary incontinence with the compound as instantly claimed, a showing of unobvious and superior properties in using the compounds for this method of treatment would also have to be shown.

WO 96/32939 discloses phenyliminoimidazolidine tautomeric equivalent derivatives of the formula Ib and II (page 2 and page 3) with preferences towards compounds substituted with hydrogen, bromine and chlorine at positions R1, R2, R3 and R5 and alkyl at position R4 (page 4 and page 5) which are useful for the treatment of urinary incontinence. Examples of alkyl as isopropyl and tertiary butyl are found on page 6, lines 13-18. DE 3712385 discloses phenyliminoimidazolidine derivatives of the formula I, page 2, whish are useful as an alpha1-adrenergic agonist, page 4, and discloses a positional isomer of the compounds as instantly claimed (page 2, line 42). These references provide a suggestion or motivation to combine the reference teachings since they both disclose phenyliminoimidazolidine derivatives that are useful for the treatment of urinary incontenence or as alpha1-adrenergic agonists. The reasonable expectation of success comes from WO 96/32939 generically encompassing that as instantly claimed and providing preferences for the substituents towards that which is instantly claimed which are useful for the treatment of urinary incontenence and from DE 3712385 disclosing a positional isomer of the compounds as instantly claimed, which is useful as an alpha1-adrenergic agonist. As can be seen

from above and from the Previous office actions the references teach and suggest all of the claim limitations.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

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